5-13-2021

Inflammation, Diet, and Depression

Kareem F. Hamada

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Department of Psychology

John F. Axelson, Ph.D., *Advisor*

Noah C. Berman, Ph.D., *Reader*

Xiaoduo Fan, M.D., M.P.H., M.S., *Reader*

A thesis submitted to the office of Scholar Programs in partial fulfillment of the requirements for graduation with College Honors at the College of the Holy Cross

May 2021

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ABSTRACT

Although it is well established that inflammation contributes to cardiovascular disease (CVD), this thesis considers the potential for dietary-induced inflammation to also play a role in the development of depression. Even though the association between inflammation and depression was initially proposed over 100 years ago, treatment of depression has focused on psychopharmacological and psychotherapy. In addition to the increases in the chronic diseases that are the leading causes of death, including CVD, diabetes, and several forms of cancer, consumption of meat, dairy, and highly processed foods have also increased dramatically in recent decades. The resulting Standard American Diet (S.A.D.) is highly inflammatory and is known to play a significant role in the etiology of CVD. In contrast, a whole food, plant-based (WFPB) diet reduces the body's inflammatory response. Recognizing there are many factors contributing to these complex conditions, is it possible that a WFPB diet that has been shown to prevent, and in some instances, reverse CVD also has the potential to play an important role in reducing the suffering of those diagnosed with depression?

REVIEW OF THE LITERATURE

I. Introduction:

This thesis examines the complex relationships between cardiovascular disease (CVD), diet, and depression. The primary goal is to consider whether the Standard American Diet (S.A.D.), which is highly inflammatory, has the potential to contribute to the etiology of both CVD and depression. It is well-established that drugs that promote inflammation lower thresholds for experiencing depressive symptoms (Kohler et al., 2016; Rosenblat et al., 2014). Is it possible that adopting a whole food, plant-based diet (WFPB) that has been shown to prevent and reverse CVD may also play a role in reducing symptoms and the development of depression? The Standard American Diet pattern, often referred to as S.A.D., is taking a devastating toll. The typical American diet contributes to many chronic illnesses that are the leading causes of death in the United States. Research has consistently demonstrated that reducing or eliminating refined, processed, and animal-based foods, including meat, dairy products, eggs, bleached flour, refined sugar, and oil, can prevent, and in some instances, reverse several serious diseases (Esselstyn, 2008; Esselstyn et al., 2014; Ornish et al., 1990; Tuso et al., 2013). Chronic diseases, including obesity, diabetes, CVD, cancer, and serious psychiatric illnesses, including depression, pose a significant quality of life and financial burdens for society. Although typically categorized apart from those "physical" illnesses, psychiatric illness cost Americans $193 billion in lost earnings (Roehrig, 2016). Is it possible that comparatively inexpensive behavioral interventions targeting diet and nutrition could help reduce the prevalence of individuals experiencing both CVD and depression? Could addressing the role of diet be part of what British Neuropsychiatrist, neuroscientist, and

author of "The Inflamed Mind" suggests is a "radically better – way of dealing with mental and physical health disorders together, rather than apart, as we currently do?" (Bullmore, 2018).

II. Depression: A Serious Mental Illness

A. Etiology & Symptoms

Major depressive disorder (MDD) is considered "major" for a reason. It is a serious and chronic mental illness associated with significant functional impairment and reduced quality of life (Hashmi et al., 2013; Otte et al., 2016). In addition to disrupting mood, MDD alters cognitive processes and a variety of behavioral patterns. A diagnosis of MDD requires meeting several criteria established by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (APA, 2013). MDD is characterized by one or more depressive episodes, occurring for at least two weeks of depressed mood or loss of interest accompanied by at least five of the following symptoms: feelings of prolonged sadness, hopelessness, loss of interest or pleasure (anhedonia), insomnia or hypersomnia, significant weight loss or weight gain, changes in cognition, vegetative symptoms, and psychomotor retardation (APA, 2013). Since MDD impacts mood, thought processes, and motor functions, depressed individuals struggle to function at school, at work, and at home.

MDD, more commonly known as clinical depression, is one of the most common mental disorders, affecting approximately one in every five individuals worldwide (Hashmi et al., 2013). The World Health Organization reports that, globally, 264 million people live with MDD, with women nearly twice as likely as men to be diagnosed with

this condition (Brody et al., 2018; GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; Kessler & Bedirhan Ustun, 2008). An estimated 17.3 million adults in the United States have been diagnosed with at least one major depressive episode. This number represented 7.1% of the adult population of the United States. As noted above, MDD impacts women disproportionately higher than men, with 8.7% rates for women compared to 5.3% for males (NIMH, 2019). Furthermore, as of 2017, an estimated 11 million U.S. adults aged eighteen or older experienced at least one major depressive episode with severe impairment, representing approximately 4.5% of all adults in the United States (NIMH, 2019). The prevalence rate of moderate to severe depression rose from 23.2% to 41.1% from 2007 to 2018 (Duffy et al., 2019). The importance of addressing this health crisis is further emphasized by recent evidence suggesting that incidence rates of MDD have tripled across all demographic groups in the United States. Those with serious mental illness also face exacerbation of symptoms and other challenges brought on by the COVID-19 pandemic (Ettman et al., 2020; Hamada & Fan, 2020).

Mood disorders, in particular MDD, are a significant source of morbidity and mortality and contribute significantly to the overall global burden of disease (Kessler & Bedirhan Ustun, 2008; Mykletun et al., 2007). Two metrics can help us better understand the impact of a particular disease on the global population: disease burden and healthy life years. The “disease burden” quantifies the amount of premature mortality or disability due to worldwide illness, accidents, and risk factors. “Healthy life years” measures the number of years that an individual is expected to live free of disability or disease. The Global Burden of Disease study (1990-2020) and the World Health

Organization projected that by 2020, MDD would be the second leading cause of healthy years of life lost, second only to ischemic heart disease (Lopez & Murray, 1998). A more recent study (2002-2030) projects that HIV/AIDS, unipolar depression, and ischemic heart disease will be the leading causes of global disease burden in 2030 (Mathers & Loncar, 2006). By 2030 MDD is projected to remain second in contributing to the loss of healthy years of life primarily due to its frequency and impact on functioning and quality of life.

In spite of the existing range of treatment options, MDD rates continue to rise. Along with increases in MDD diagnoses, there has been a steady increase in the amount of money spent on treatment in the United States, a testament to the economic burden associated with MDD (Birnbaum et al., 2010; Hidaka, 2012; Kessler, 2012). Contributing to the financial burden to our society is the fact that those suffering from and receiving treatment for MDD frequently receive treatment for other comorbid conditions (Greenberg et al., 2015).

Although Americans are spending more on healthcare, our citizens are sicker than ever. In 2017 alone, the United States spent approximately $3.5 trillion, or 18 percent of GDP, on health expenditures – more than twice the average among all other developed countries (Forks over Knives, 2016). Increased spending on healthcare in general and mental healthcare, in particular, would appear to be justified. However, healthcare spending for both physical and mental illness in the United States has increased significantly and now accounts for more than 17% of the United States economy, approximately $2.4 trillion dollars (Dieleman et al., 2016). By 2013, Americans spent $7.1 billion dollars on treatment of MDD, including individuals' out-of-pocket costs as

well as spending by both private and government insurance programs. Expenditures include ambulatory care, inpatient care, emergency care, and nursing/group home facility care – all these efforts targeting those living with MDD. Total expenditures for treating MDD rank sixth behind diabetes mellitus ($101.4 billion), ischemic heart disease ($88.1 billion), and hypertension ($83.9 billion; Dieleman et al., 2016). Although we are spending more money, the number of people suffering from MDD continues to rise, and our understanding of the mechanisms surrounding its etiology remains unclear.

MDD is not a homogenous condition. Each person experiences MDD in their own way, and it is likely that there are several different subtypes of this disorder. Symptoms vary from mild to severe. In more severe cases, MDD may lead to suicidal ideation and completed suicides. An estimated fifty percent of the world's yearly 800,000 suicides occur during a depressive episode, and individuals with a MDD are nearly 20 times more likely than the general population to complete suicide (Chesney et al., 2014; Otte et al., 2016).

For those experiencing MDD, an increased risk for suicide is not the only concern. Those who experience MDD have an overall increased mortality risk of 50% compared to the general population (Cuijpers et al., 2014). In short, those who experience MDD are likely to endure other comorbid chronic conditions and die sooner than the general population (Pratt et al., 2016; Walker et al., 2015). It is well established that those diagnosed with MDD are at an increased risk of developing CVD, diabetes mellitus, hypertension, obesity, cancer, Parkinson's disease, and Alzheimer's disease (Penninx et al., 2013). The complex relationship between MDD and this wide range of illnesses is poorly understood. It is not surprising that those suffering from significant medical

challenges are at increased risk of MDD. However, a more complete understanding of the relationship between mental and physical disorders remains unclear. For individuals with MDD, changes in diet, reduced physical activity, disruption of sleep/wake cycles, and increased consumption of alcohol and drugs have the potential to contribute to the development of many chronic illnesses. In addition to how those changes in behavior and lifestyle contribute to the relationship between MDD and what are considered "physical illnesses," it is also possible that MDD and a wide range of illnesses share other common etiologic factors. Could systemic inflammation, known to contribute to the development of a wide array of physical illnesses, also contribute to MDD? (Furman et al., 2019). It is likely the body's inflammatory response contributes to the etiology and experience of both CVD and MDD.

B. Current Treatments for MDD

Treatment of MDD falls into two broad categories: psychopharmacology and psychotherapy. Psychopharmacological therapies include antidepressant medications such as serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs; Hashmi et al., 2013; Otte et al., 2016). Alternatively, psychotherapies include cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and problem-solving therapy as well as a variety of other lifestyle interventions (dietary modification, lifestyle education programs, mindfulness-based therapies, etc.). Success rates for antidepressant medications vary between different medication categories and depend on the degree of severity of depressive symptoms. While the efficacy of antidepressant medications is well established for the most severe forms of depression, some critics suggest that drug treatment for mild to moderate

depression is not reliably better than placebo controls (Kirsch et al., 2008). However, a recent study examined the efficacy of 21 antidepressant medications (all targeting serotonin or noradrenaline circuitry) and found that all medications appeared to exhibit moderate effects compared to placebo (Cipriani et al., 2018). Given the wide range of how those with mild to moderate depression respond to antidepressant medications, efficacy for any given individual is difficult to predict.

Recovery rates appear to increase when CBT is used as an adjunct to antidepressant treatment (Driessen & Hollon, 2010). Still, approximately one-third of individuals with MDD experience refractory symptoms, characterized by recurrent, prolonged cycles of severe, and in some cases, depressive episodes that do not remit despite multiple treatment attempts (Hashmi et al., 2013; Otte et al., 2016). For treatment-refractory patients who have not responded to antidepressant treatment or a combination of antidepressants with psychotherapy, 70 to 90 percent of those patients benefit more from electroconvulsive therapy (Mennitto, 2019; Otte et al., 2016). For many, despite access to existing treatment options, MDD lingers (Bai et al., 2020; Rush et al., 2006). Moreover, new evidence raises concern that suicide might be facilitated by antidepressants in the adolescent population (Gunnell & Ashby, 2004; Healy, 2003). Although progress has been made, existing treatments, both psychopharmacological and psychotherapies, are not helping as much for those suffering from MDD as one would hope. It is important to note that there are new novel approaches to treating MDD including augmentation agents (e.g., ketamine) and repetitive transcranial magnetic stimulation (rTMS). Although some studies show encouraging results, more research is necessary to determine the efficacy, safety, and utility of these new treatment options

(Chen et al., 2020; Shiroma et al., 2020). Taken together, it is clear that no single treatment is likely to solve such a complex and varied condition as MDD.

III. Risks of Adopting the Standard American Diet (S.A.D.)

A growing body of evidence supports the conclusion that the S.A.D., or what is referred to as the western diet, is a significant factor in the widespread increase of CVD (Colin Campbell, 2013; Esselstyn, 2008; Naidoo, 2020). As noted earlier, MDD is a common comorbidity for those suffering from CVD, and it is likely the western diet contributes to the development of both CVD and MDD.

Immigrants appear to be at increased risk for several illnesses, particularly CVD and MDD (Lesser et al., 2014). Cultural and societal pressures appear to contribute to the increased incidence rates of MDD, which disproportionately impacts immigrant and lower socioeconomic populations. Two-thirds of Mexican immigrants who immigrated to the United States in the 1990s or earlier were forced to adopt a dramatically different diet from their country of origin. Interestingly, as recently as 1994, the prevalence of obesity among adults was only 10% in Mexico, compared to 26% in the United States. Maintaining the lifestyle of one's country of origin, including dietary habits, might act as a protective buffer for immigrants (Barquera et al., 2008; Van Hook et al., 2018). Dietary acculturation, specifically the adoption of western dietary habits, puts immigrants at risk for many illnesses, including obesity and Type II diabetes (Lesser et al., 2014). Immigrating at a younger age increases the risk for MDD, and surprisingly, the longer one lives in America, the more at-risk immigrants become for experiencing MDD. Public health officials suggest that as immigrants from non-western countries assimilate and

adopt the health habits of their new western communities, including high-fat diets and processed foods, along with reduced physical activity, an immigrant's health declines. Unfortunately, most low-income countries now have access to the processed foods Americans have been eating for several decades (Gordon, 2015).

The negative health impacts of social and cultural changes are not limited to those immigrating to America. Many are moving from rural areas into metropolitan centers in China, and both MDD and chronic physical illnesses, including CVD, are on the rise (Bei et al., 2018). Chinese individuals born after 1966 are twenty times more likely than those born before 1937 to suffer from a major depressive episode during their lifetime (Lee et al., 2007). China's population is aging and chronic diseases including CVD, obesity, and liver and lung cancers are increasing in prevalence. The shift in dietary pattern in China from the traditional, primarily plant-based diet and adopting increasing amounts of foods found in the western diet appears to have played a significant role in the changing health status in this country (Colin Campbell, 2013; Colin Campbell, 2006; Pan et al., 2012; Thomas et al., 2020). As a result, China has seen an epidemiological shift in morbidity and mortality from diet-related diseases. Additionally, the incidence rates of many mental disorders, including MDD, have increased significantly over the last 30 years (Huang et al., 2019). Although the focus of this thesis is on diet, it is important to note that many other factors (e.g., reduced physical activity levels) associated with adopting modern western culture can contribute, in complex ways, to the increasing number of people experiencing MDD throughout the world.

Although MDD occurs in many forms, it tends to fall into two broad categories: early-onset (before age 30) and late-onset (after age 35). Those diagnosed with MDD

after age 35 have a high probability of having relatives who have CVD (Kendler et al., 2009). Over time, the S.A.D. contributes to the development of plaque in our arteries in response to inflammation that is the key component of CVD. The fact that those diagnosed with MDD later in life are likely to come from families that also suffer from CVD raises the question; how might diet contribute to the development of both illnesses?

A. The Complex Relationship Between CVD and MDD

Individuals suffering from MDD have an increased risk of CVD. In some cases, MDD significantly worsens prognosis for recovering from CVD (Lauzon et al., 2003; Stewart et al., 2014). Individuals with MDD that are also diagnosed with CVD have a one to three-fold increased risk for additional cardiac events within two years (Barth et al., 2004; Meijer et al., 2013; Meijer et al., 2011; Nicholson et al., 2006). Conversely, having a history of CVD is associated with increased risk of MDD. Several meta-analyses indicate a strong positive correlation between CVD and MDD (Nicholson et al., 2006; Rugulies, 2002; Ski et al., 2016; Van der Kooy et al., 2007). Most importantly for the current discussion, MDD and CVD are both linked to several dietary-related risk factors including diets rich in calorically dense foods, obesity, and diabetes (Frasure-Smith & Lespérance, 2010; Skala et al., 2006). Many researchers have suggested that the association between MDD and inflammatory markers is a critical biochemical link in the comorbidity of MDD and CVD (Goldston & Baillie, 2008; Joynt et al., 2003; Lippi et al., 2009; Paz-Filho et al., 2010; Raison et al., 2006). These findings further support the need for a more holistic approach to MDD that includes treating both the body and the mind.

B. Mental and Physical Illness: A False Dichotomy

How have mental and physical illness come to be viewed as separate entities? The 17th century French Philosopher René Descartes's dualistic approach separated the physical body and non-physical or spiritual mind. As a result, western medicine typically separates illness into either impairment of physical or mental dimensions. Put simply, the Cartesian dualistic perspective describes two domains of our experiences. The first domain is the outer, physical world, in which objects interact with each other mechanistically. For example, simple spinal cord reflexes represent physical responses to external stimuli. The second domain is the inner, spiritual world, in which emotions form our thoughts and sense of self (Gendle, 2016). Cartesian dualism, therefore, separates the objective physical body from the spiritual and subjective mental realm. When discussing symptoms of most illnesses, it is common for people to ask: "Is the problem physical or psychological/mental?" When someone with a serious physical illness becomes depressed, the depression is most often interpreted as a psychological reaction to the knowledge and experience of being physically ill. As noted earlier, MDD is common for those with CVD, with the prevalence of MDD among cardiac patients ranging from twenty to thirty percent (Thombs et al., 2006). Although they frequently occur together, "Cartesian medicine" has promoted the belief that the mental and physical illnesses develop independently. It is possible that in addition to the psychological reaction to experiencing physical illness contributing to MDD, these "mental" and "physical" illnesses share common causal factors related to diet and inflammation (Bullmore, 2018).

In a way it is strange to assume that problems in our body, in this case the cardiovascular system, occur independent of the mental experience of MDD. Separating

the physical and mental domains makes it less likely to consider the individual as a whole, and a consideration of the possibility that both the physical and mental disorders share common causal factors. Edward Bullmore describes the dualist approach in western medicine as synonymous to "medical apartheid." We should consider novel treatments that target and move towards understanding the body and mind as one. The emphasis of this thesis is to consider the potential for dietary related inflammation to connect and influence both the mind and the body.

IV. Inflammation and Depression

A. Did Depression Evolve as Part of the Inflammatory Response?

The evolutionary theory of MDD suggests that MDD evolved as an advantageous response to inflammation and infection (Anders et al., 2013). Depressive behavior may have been an adaptive response to help individuals as they fight off, and attempt to survive, infection or injury. The infection-defense hypothesis considers MDD as a beneficial "sickness-like" behavior that includes social withdrawal, anhedonia, fatigue, hypersomnia, and psychomotor retardation. The symptoms and behaviors observed in MDD, such as anorexia, weight loss, decreased locomotor activity and exploration, fatigue, sleepiness, and inability to concentrate, are also seen in sickness behavior. Withdrawing from contact with others reduces the risk of infection or transmitting infectious diseases to other genetically related individuals. Self-isolating behavior, which is common in both depression and sickness behavior, also allows one to conserve energy and promotes restfulness to help the individual have a better chance of fighting off the infection and enhancing recovery (Maes et al., 2012). Reduced activity helps recovery by

conserving energy while dealing with the inflammatory response. Put simply, when we become infected and our immune system responds by releasing pro-inflammatory cytokines, we feel lousy, sick, weak, and fatigued. In essence, we act as though we are depressed when we are ill (Anders et al., 2013). An important distinction between sickness behavior and depressive symptoms is that sickness behavior is an acute, short-term state in response to an acute inflammatory response, whereas depressive behavior may be the result of more chronic, long-term accumulation of inflammation in the body that has gone unnoticed (Maes et al., 2012).

If the association between inflammation and MDD evolved because the depressive response to inflammation was advantageous, then we should expect to see that the genes for an increased risk of MDD are related to individual differences in one's immune system. It is well-established that MDD runs in families; people whose parents were diagnosed with MDD are three times more likely to suffer from MDD than those who do not have a parent with MDD (Dunn et al., 2015; Sullivan et al., 2000). However, families share more than genes. It is likely that children learn how to become depressed from living with a depressed parent (Loechner et al., 2020; Rishel, 2012). Also, research linking specific genetic profiles to MDD is inconclusive. A recent study attempting to provide a genetic map for MDD suggests that the human genome includes at least forty-four "genes for depression," including several genes that play a role in the immune system (Wray et al., 2018). Although additional studies are needed, these findings support the suggestion that inflammation may be one of many underlying factors contributing to MDD and further emphasize the importance of holistic treatment of both

mental and physical disorders. We should consider the bigger picture including our current lifestyle, the western diet.

B. The Inflammatory Response

Inflammation is a natural part of the body's immune response to infection by a pathogen (i.e., a bacteria or virus), or tissue damage (i.e., physical injury; Chen et al., 2018). Inflammation can occur as an acute and short-lived response or be part of a long-lasting, chronic condition. An acute inflammatory condition occurs in response to a pathogen or injury. In this case, when the pathogen is no longer present or the injury is resolved, the inflammatory response ends. However, when the inflammatory response is prolonged, the response is systemic, meaning inflammation occurs throughout the body. As a result, chronic inflammation has the potential to contribute to a wide array of chronic or systemic illnesses, including CVD (Zhong & Shi, 2019).

The acute inflammatory response is familiar to anyone who has suffered either a minor or severe injury. Both a paper cut and a major strain result in inflamed, red, and painful tissues – all part of the body's healing process. The five signs of inflammation were first identified by Celsus in Roman times: redness (rubor), swelling (tumour), heat (calor), pain (dolor), and loss of functions (functio laesa; Bullmore, 2018). In response to infection our immune system releases white blood cells into the bloodstream and tissues to protect the body from foreign invaders. The inflammatory response increases blood flow to the area affected by injury or infection causing redness and warmth. Chemicals released from our white blood cells cause fluid to leak into tissues, resulting in the familiar sign of swelling or inflammation (Punchard et al., 2004). If it were not for our

body's inflammatory response, we would be left defenseless against infectious diseases, tissue damage, or physical injury.

Although we benefit from acute inflammation, we now know that chronic inflammation plays a role in many chronic illnesses (Furman et al., 2019). Chronic inflammation is associated with gut dysbiosis (leaky gut syndrome), CVD, obesity, metabolic syndrome, diabetes mellitus, and several types of cancer. Symptoms of chronic inflammation differ from the symptoms of acute inflammation and include fatigue, fever, rashes, abdominal pain, and chest pain. Although one can easily understand and visualize an acute inflammatory response, the long-term chronic inflammatory response is more difficult to appreciate and address.

Medical conditions associated with chronic inflammation can be considered within two categories; those which are directly related to diet and those that are considered outside the role of diet and digestion. Obesity is first on the list for conditions associated with dietary-related inflammation. Excess adipose tissue releases inflammatory mediators and as a result, obese individuals exist in a chronic state of systemic inflammation (Calder et al., 2011). A second dietary condition related to the inflammatory response is microbiome-dysbiosis, or the disruption of the microbiome in the gut. Leakage of bacteria from the intestinal tract directly into the bloodstream activates immune cells and contributes to a pattern of chronic inflammation. It may be possible that chronic inflammation associated with obesity and leaky gut may contribute to the etiology of depressive symptoms. Could adopting a less inflammatory diet reduce the risk for developing MDD?

Consumption of vegetables, fruits, whole grains, and legumes have been shown to reduce inflammatory biomarkers including Interleukin 6 (IL-6) and C-reactive proteins (CRP; Lopez-Garcia et al., 2004). In contrast, consumption of large amounts of red meat and processed-refined foods elevate levels of inflammatory markers (Lopez-Garcia et al., 2004). Consumption of large amounts of animal products and heavily processed foods is associated with higher levels of CRP, while the Mediterranean diet that emphasizes whole foods and fruits and vegetables is associated with lower inflammatory markers (Fung et al., 2001). Much of the S.A.D. is inflammatory and, as a consequence, has the potential to impair the immune system (Myles, 2014). Examples of pro-inflammatory foods include fried and highly refined and processed foods containing added sugars that elevate CRP. Sucrose-rich processed foods consistently increase inflammatory biomarkers (Jenkins et al., 2003). In contrast, whole grains such as millet, quinoa, and barely, with a low glycemic index appear to promote healthy immune function, established by measuring changes in intestinal microbiota as microbial changes in the gut have often been associated with inflammatory status in the body (Parikh et al., 2012; Tachon et al., 2013; Volman et al., 2008).

In addition to highly processed and sugary foods that elevate blood glucose levels and increase biomarkers for inflammation, much of the S.A.D. contains large amounts of inflammatory fats and oils. Processed and fried foods containing omega-6 fatty acids and trans-fatty acids increase the production of pro-inflammatory cytokines and as a result promote inflammation (Rangel-Huerta et al., 2012; Simopoulos & Cleland, 2003). Dietary interventions show inflammatory biomarkers can be reduced by simply changing what we eat. Participants randomly assigned to a diet rich in fruits and vegetables (eight

servings a day) for eight weeks had significantly lower CRP levels than those who consumed two or less servings a day (Watzl et al., 2005).

Apart from those dietary and digestive conditions long term chronic inflammation occurs with the following conditions: chronic stress, untreated infections or injuries, autoimmune diseases in which the immune system attacks healthy tissue, Hepatitis (i.e., inflammation of the liver), and a wide array of medical interventions including surgeries, radiation, and chemotherapy. It is not surprising that MDD is also more likely for those suffering from all those conditions in which chronic inflammation occurs.

C. Inflammation Triggers Both Physical and Depressive Symptoms

Fortunately, in recent years, questions bridging the gap between the field of psychiatry and diet-related immunology (immuno-psychiatry) are now being asked: "How can inflammatory changes in the body affect our mood, cognition, and behavior?" "How can our immune system, which is built to help protect us, make us depressed?" (Dantzer et al., 2008; Maes, 1995; Raison et al., 2006; Smith, 1991).

Inflammation is not typically associated with changes in mood. As stated earlier, acute inflammation is the response of the immune system to an infection or threat. White blood cells known as macrophages attack and engulf bacteria and other infectious pathogens. Macrophages also secrete proteins into the bloodstream known as cytokines, which circulate throughout the body further alerting the rest of the immune system response. Therefore, macrophages play two distinct roles: 1) deal directly with the infection at the afflicted site and respond as necessary, and 2) amplify a signal to the rest of the body, encouraging the release of more immune cells into the bloodstream to assist in attacking the infection. Most importantly for the current discussion is the fact that

cytokines act within the central nervous system to produce the psychological components of fatigue, fever, and decreased appetite; the symptoms we are familiar with when we are sick. It is now known that the inflammatory response impacts the central nervous system, with the potential to influence neural circuits controlling affect and mood (Olofsson et al., 2012).

The "coincidence" of MDD and inflammation is actually quite common. Individuals with rheumatoid arthritis, an auto-immune and inflammatory disease, are two to four times more likely to experience depressive symptoms (Margaretten et al., 2011). Similar to the previous discussion of MDD occurring in response to diagnosis of heart disease, it is not surprising that those who have been diagnosed with an auto-immune disease, and are experiencing chronic pain, report that they are also sad and depressed. As stated previously, in these instances it is commonly assumed that the immune system that is responsible for the physical symptoms occurring within the body, while the symptoms of MDD are simply the result of psychological interpretations (taking place in the brain) of those bodily changes. Until recently, the brain and immune system were thought to be separated by the Blood Brain Barrier (BBB), a network of cells that acts as a selective filter. In the case of the inflammatory response, the BBB was thought to prevent macrophages and cytokines circulating in the body from reaching the brain. Thus, the brain was thought to be protected and separated from the inflammatory response occurring in the body. However, discoveries in recent decades provide evidence demonstrating inflammatory cells, as well as other proteins including CRPs cross the blood brain barrier and act upon brain cells (e.g. microglia) which initiate an inflammatory response within the brain itself. Not surprisingly, an increase in

inflammatory cytokines in the blood and in the cerebrospinal fluid is predictive of an increase in symptoms of MDD (Berk et al., 2013; Bullmore, 2018; Hashmi et al., 2013). Following cytokine administration, healthy individuals experience somatic symptoms such as fatigue, aches, pains, loss of appetite, and even insomnia (Rosenblat et al., 2014). Up to 50% of those who received cytokines developed symptoms of MDD, including but not limited to depressed mood, feelings of guilt, worthlessness, and suicidal ideation (Rosenblat et al., 2014). Thus, the inflammation that initially occurred within the body has the potential to impact the brain in multiple ways that may contribute to the development of symptoms of MDD. It is worth noting that individuals with elevated levels of these inflammatory biomarkers are less likely to respond to antidepressant treatment particularly SSRIs (Haroon et al., 2018).

If inflammation has the potential to contribute to the experience of MDD, we should expect inflammation to precede the onset of depressive symptoms and that evidence exists. Inflammation early in life appears to precede depressive symptoms. Khadaker et al. (2014) assessed biomarkers for inflammation in young individuals. Data were collected from nine-year-olds who were not depressed, and again nine years later. Accordingly, higher levels of the systemic inflammatory biomarkers, specifically IL-6, in childhood were associated with an increased risk of developing MDD in young adulthood (Khandaker et al., 2014).

It is important to stress that this thesis is not suggesting dietary changes that reduce inflammation will solve all the problems associated with a disorder as complex as MDD. Rather than consider MDD as an inflammatory disorder, it is more likely that depression is a response to inflammation. Since not everyone who is depressed shows

evidence of chronic inflammation, it is more likely that inflammation may be one of many contributing factors that lowers the threshold for MDD in a particular subset of individuals. Thus, while the emphasis here is on the potential role of diet-induced inflammation, it is important to stress that many factors contribute to the onset and development of MDD.

V. The Impact of the Standard American Diet

The S.A.D. is a major contributor to obesity, anemia, osteoporosis, Type II diabetes, hypertension, and several forms of cancer (Jacka et al., 2010). Previous diets that emphasized non-processed fresh foods that are high in fiber, nutrient-dense foods, and omega-3 polyunsaturated fatty acids have been largely replaced by diets high in saturated fats and refined sugars (Drewnowski & Popkin, 1997). In addition to the chronic illnesses mentioned above, there is no longer any doubt that the S.A.D., high in unhealthy fats and sugar, is a key factor in the development of atherosclerosis (i.e., hardening of the arteries) – the underlying mechanism of CVD. Dr. Caldwell Esselstyn, author of, "Prevent and Reverse Heart Disease: The Revolutionary, Scientifically Proven, Nutrition-Based Cure" summarizes how the S.A.D. sets the stage for heart disease (Esselstyn, 2008).

The typical S.A.D. elevates cholesterol, in particular low-density-lipoproteins which are the basis for plaques forming within blood vessels. Once plaques begin to impair blood flow, inflammatory enzymes attempt to thin or reduce the build-up of plaque. If and when plaque is dislodged from a blood vessel, their presence in our blood activates the release of clotting factors known as platelets, which increase risk further by

making our blood "sticky." Heart attacks occur when plaques block arteries that supply the heart with oxygen and necessary nutrients it needs and begins to die. As a result of how poorly many children now eat, recent studies demonstrate that plaque begins to accumulate in the arteries as early as age ten, resulting in chronic inflammation (Hong, 2010). Given that atherosclerosis begins in childhood, and progresses during adolescence and young adulthood, it is no surprise that individuals raised on the S.A.D. already have "fatty streaks" within their arteries, the first stage of CVD (McMahan et al., 2006). Such "fatty streaks" then turn into plaque when people are in their 20s and over the next decade or two have the potential to form life-threatening blockage of arteries. Fortunately, dietary changes have been shown to prevent, and even reverse, this key pattern of CVD (Esselstyn, 2008).

It may come as a surprise to many that consuming a single meal high in animal-based saturated fat produces an inflammatory response, which significantly reduces arterial blood flow (Erridge et al., 2007; Plotnick et al., 1997). Within hours of consuming significant amounts of saturated fat, the arteries become nearly "paralyzed," cutting blood flow in half. Even if the body has a few hours to recover, if the next meal also consists of meat, poultry, eggs, or dairy (all high in saturated fat) the result is even more inflammation. Consequently, the bodies of many people consuming the S.A.D. are trapped in a state of chronic, low-grade, diet-induced inflammation.

Fortunately, individuals diagnosed with CVD that adopt a WFPB diet that reduces or eliminates most animal-based foods, show improved cardiovascular functioning, without the use of statin drugs or surgery (Esselstyn, 2008). In the landmark Lifestyle Heart Trial, 82% of individuals diagnosed with CVD who adhered to a WFPB dietary

pattern had significant regression of disease after just one year, marked by 40% decrease in lipoprotein, a precursor of plaque (Ornish et al., 1990). Is it possible for the dietary changes that reduce the chance for and promote recovery from CVD, also be used to treat and prevent MDD? Even though dietary induced inflammation may play a role in the development of both CVD and MDD, it is important to recognize that inflammation is not found in all those who experience MDD. Thus, a dietary approach is not a one-size-fits-all solution to MDD.

VI. The Whole Food, Plant-Based Diet

The WFPB diet is often confused with vegetarian and vegan diets. As defined by Dr. T. Colin Campbell, a WFPB diet is centered on whole, unrefined, or minimally refined plants. It is a diet based on nutrient-dense fruits, vegetables, tubers, whole grains, and legumes; and it excludes or minimizes meat (including beef, poultry, and fish), dairy products, eggs, and highly refined foods such as bleached flour, refined sugar, and oils (Colin Campbell, 2013; Pulde et al., 2019). Vegetarian and vegan diets are defined on the basis of what is not eaten rather than what is eaten. Therefore, as long as they eliminate animal products from their diet, vegetarians and vegans are free to eat highly processed foods. Although leaders in the field of WFPB diets have varying opinions as to what the optimal WFPB diet is composed of, Dr. Dean Ornish recommends small amounts of certain animal-based products such as egg whites and skim milk (Ornish et al., 1990). In contrast, Dr. Caldwell Esselstyn recommends complete avoidance of all animal-based foods as well as soybeans and nuts for those with severe CVD (Esselstyn, 2008). In spite of these variations in the composition of a WFPB diet, evidence suggests that a broadly defined plant-based diet has significant health benefits (Tuso et al., 2013).

There are five major food groups in a WFPB diet including fruits, vegetables, tubers, whole grains, other starches in "whole form," and legumes (**see Figure 1**; Stone, 2011). There are several other types of plant-based foods one can consume such as nuts, seeds, avocados, tofu, tempeh, whole-grain flours and breads, and plant-based milks; however, because these foods are more calorie-dense, and can contribute to weight gain and mild inflammation, it is recommended that these be consumed in moderation. Most people adopting a WFPB diet are able to consume foods *ad libitum*, meaning they can eat as much as they desire – no need for calorie counting or portion control. The main focus of a WFPB diet is to improve the quality of the food one consumes, rather than restricting the quantity of the food. This may be a more suitable intervention for those who are suffering from MDD as compliance is a major challenge for those attempting to adopt a new diet. Since there are less published results concerning strictly WFPB diets, this review will incorporate findings based on what are classified as a "Mediterranean Diet" since they emphasize plant-based, unprocessed foods.

A. Inflammation and the Whole Food, Plant-Based Diet

As previously mentioned, CRPs, a biomarker of inflammation, are elevated in individuals suffering from MDD, as well as CVD as CRPs are indicative of inflammation in the bloodstream. Adhering to a WFPB diet can decrease CRP levels by 30% within just two weeks (Jenkins et al., 2003). Given that a WFPB diet is rich in fruits and vegetables, it is associated with lower inflammatory markers due to the anti-inflammatory properties of antioxidants (Michael Maes et al., 2011). Accordingly, recent studies have shown that antioxidants combat neuro-inflammation caused by free radical damage, which is thought to be a precursor to several psychiatric illnesses including MDD and

anxiety disorders. By reducing free radicals, we reduce inflammation, and in turn, improve symptoms of MDD (Berk et al., 2013).

Several studies have found that limiting processed and refined foods is important in reducing one's risk for or prevention of MDD; however, incorporating diet as part of the treatment of MDD has yet to be elucidated. A recently published meta-analysis provides evidence that a balanced plant-based dietary pattern (e.g., Mediterranean, whole-food, plant-based, vegetarian, or vegan, etc.), lowers one's risk for MDD, and demonstrated that improvement in diet significantly reduced depressive symptoms (Firth et al., 2019; Molendijk et al., 2018). Findings are encouraging, but to our knowledge, there have been only two extensive randomized controlled trials (RCTs) in adults with MDD – the SMILES (Supporting the Modification of lifestyle in Lowered Emotional States) trial, and the HELFIMED (Healthy Eating for Life with a Mediterranean Diet) trial (Jacka et al., 2017; Parletta et al., 2019). The results of the SMILES trial demonstrated that individuals in the dietary intervention group, that emphasized plant-based foods, had a larger reduction in depressive symptoms over the three-month study period when compared to those in the social support control group. By the end of the SMILES trial, 32.3% of individuals in the dietary intervention group met criteria for remission of MDD over twelve weeks when compared to the 8% in the social control group.

The findings of the SMILES trial are consistent with, and further support, the findings of the HELFIMED study, which also examined the use of diet for the treatment of MDD. The HELFIMED trial evaluated a group-based dietary intervention supplemented with omega-3 fish oil supplements, similar to the SMILES trial, and

conducted cooking workshops for adults with self-reported depressive symptoms. The dietary protocol of the study mirrored that of a Mediterranean-style diet that limited meat and dairy while emphasizing fresh fruits and vegetables. Three months following the dietary intervention, individuals in the dietary group showed significant reductions in depressive symptoms and improved mental health outcomes when compared to a social support control group. Surprisingly, dietary improvements were sustained at six months following the intervention when individuals were reassessed. The adherence of depressed individuals to dietary protocol after the study's termination is promising as treatment adherence is often challenging for individuals with serious mental illness, in particular MDD (Sirey et al., 2017). Adherence to dietary advice is typically very poor even for the general population, so the fact that individuals in the dietary intervention group were able to adhere to diet recommendations is encouraging (Francis et al., 2019). One possible explanation for increased dietary adherence is the fact that in plant-based nutrition, individuals are encouraged to consume foods *ad libitum*. Another possible explanation is that the Mediterranean diet is a highly palatable diet, and includes a variety of food options, making it more likely to become a sustainable part of a healthy lifestyle (Bach-Faig et al., 2011; Parletta et al., 2019).

Containing significant amounts of fiber that provide satiating bulk, plant-based foods help terminate hunger signals (Pulde et al., 2019). Put simply, the strategy of plant-based nutrition is to improve the quality of the food rather than restricting the quantity of food because, usually, a major challenge for individuals attempting dietary restrictions. Also, "diets compel us to fixate on restriction and portion sizes, leaving us feeling hungry and miserable...worst of all, diets rely on "willpower," that elusive virtue that will almost

always crumble, right along with our self-confidence," which further explains adherence in the aforementioned studies; since consumption is unrestricted participants may feel more compelled to follow-through with a dietary intervention plan (Pulde et al., 2019).

In addition to the RCTs conducted in adults, a brief dietary intervention with a younger population of depressed individuals showed that increased consumption of plant-based foods reduced symptoms of MDD. Although this particular intervention lasted only three weeks, participants' dietary changes were maintained for three months following the intervention (Francis et al., 2019). All three RCTs, the SMILES trial, the HELFIMED trial, and brief dietary intervention for young adults had similar diet protocols, advising individuals in the dietary intervention groups to increase consumption of vegetables, fruits, whole grains, nuts, and seeds, and decrease consumption of highly process and refined foods. Additional RCTs including the PREDIMED (Prevención con Dieta Mediterránea) study which successfully implemented the Mediterranean diet in adults with high cardiovascular risk. Most importantly for the current discussion is that in addition to reducing the risk for CVD, the dietary intervention of the PREDIMED study also decreased the risk of participants experiencing depressive symptoms (Zazpe et al., 2008).

It should be noted that the dietary interventions in the studies mentioned above included fish, fish oil supplements, and other oils like olive oil in their diet protocols. Nevertheless, in addition to meat and dairy, consumption of fish and all oils have the potential to contribute to chronic, systemic, low-grade inflammation since fish has as much cholesterol as beef, poultry, and pork (Parletta et al., 2019; Pulde et al., 2019). Therefore, although the Mediterranean diet appears to be a significant improvement from

the S.A.D., it does contain foods that should be consumed in moderation. A WFPB diet advises against inclusion of fish, oils, and other dietary supplements (i.e., fish oil) as some studies have demonstrated that omega-3 found in fish is pro-inflammatory (Lucas et al., 2014). Consumption of fish was associated with increased CRP levels; consistent with recent findings that omega-3 fatty acids do not appear to help with improving either MDD or inflammation and was also found to be ineffective in preventing CVD (Bloch & Hannestad, 2012a, 2012b). Furthermore, the HELFIMED study which provided individuals with fish oil supplements found no significant correlation between increased omega-3 and improved depressive symptoms (Parletta et al., 2019). Therefore, adopting a WFPB diet excluding (or limiting) intake of fish as well as single nutrient supplements (i.e., fish oil) is likely to have far greater benefit for both CVD and MDD.

As is the case for antidepressant medications that include side effects such as impotence, there are side-effects for adopting a WFPB diet. The side effects include loss of excess weight, decreased risk of developing several chronic illnesses, and moving to an ideal weight. Unlike impotency, these are side effects that you want.

VII. Conclusion and Future Directions

Obviously, our current approaches to MDD are not as effective as one would hope, and they are not sustainable. With all the available treatment options for MDD from new medications to psychotherapy, and all the expenses, there is escalating mortality and morbidity. The focus of this thesis has been to consider incorporating a dietary approach to reduce inflammation in our attempts to help those experiencing MDD. Most significantly, diet is a malleable risk factor, making it amenable to intervention and preventative strategies.

Although we may not be able to cure all chronic inflammatory diseases, including CVD and MDD, implementing primary prevention strategies such as a WFPB dietary intervention may allow us to both manage existing symptoms and prevent exacerbation of symptoms (Tuso et al., 2013). Given that we understand that inflammation plays a potential role in the etiology of MDD, implementing an anti-inflammatory diet allows for a more personalized treatment approach for individuals with MDD (Kohler et al., 2016).

There are several benefits to collaborative dietary decision-making on one of the hallmark symptoms of MDD, hopelessness, which is encouragement of individuals to play an active role in decisions concerning their health and mental well-being. By encouraging involvement in making dietary changes, it provides an increased sense of self-efficacy, an important factor that has the potential to contribute to improved affect, independent of the nutrition changes in the body. A possible way to facilitate transition to a WFPB diet is a shared-decision-making process (SDM). Implementing a SDM process allows both healthcare professionals and individuals with MDD to jointly assess dietary intervention plans, and agree on a treatment that works for both the healthcare provider and individual (Desroches et al., 2011). This method of intervention is an ideal strategy for encouraging adherence to dietary advice, a critical component in preventing and managing treatment plans. Using SDM as an intervention is particularly relevant to those with MDD as it may enhance self-efficacy, provide a sense of control, and empowerment, allowing them to overcome helplessness and hopelessness (Raue et al., 2010). An individual participating in their own treatment plan can also improve outcomes as small improvements in diet quality has been associated with promoting resilience (Lutz et al.,

2017). Making dietary changes is a challenging, yet empowering approach to early prevention and intervention.

For those with MDD, quality of life should be a primary concern. In addition to poor diet, individuals with serious mental illness, in particular MDD, lack an adequate understanding of the effects of poor lifestyle behaviors on health (Parletta et al., 2019). It is important to acknowledge that not everyone has the same opportunity to eat healthier as financial barriers, and inadequate access to resources, remain a challenge for those living with serious mental illness (Cheung et al., 2021). Those living in lower socioeconomic environments, in what are referred to as "food deserts," may not have the opportunity and financial resources to make healthier food choices. When the only store an individual has access to is a convenience store, they are not likely to find fresh fruits, vegetables or unprocessed whole foods. Food insecurity is associated with the degree to which diet influences immune-inflammatory pathways, which as previously mentioned, may have an etiological role in the development of mood disorders, particularly MDD (Bergmans et al., 2018).

The Physicians Committee for Responsible Medicine has proposed significant changes in the current SNAP program (Supplemental Nutrition Assistance Program) aimed at helping those lacking adequate access to healthier food choices. It is widely believed that the cost of plant-based foods is too expensive; however, analyses are based on cost per calorie without any consideration for nutritional value (Flynn & Schiff, 2015; Springmann et al., 2016). There is no doubt that based on cost per calorie, calorically-dense foods high in saturated fat and sugar are cheaper. Although the current SNAP program does very little to assure proper nutrition, the Physicians Committee for

Responsible Medicine has suggested stores that accept SNAP payments should be required to offer healthier foods, and they suggest that people can spend $1 on any food of their choosing including junk food, or they can convert that $1 into $3 that can be used to purchase fresh fruit and vegetables. It is clear that further effort is needed to make plant-based diets more widely available to lower socioeconomic populations as adherence to dietary advice has been shown to vary according to socioeconomic status.

Accepting that those experiencing food insecurity have less access to eat healthier whole plant-based foods, we need to make the necessary changes in our food distribution systems and government support agencies to partner with those who have less access to healthy food options to assure that they too have the opportunity to gain an increased sense of self-efficacy that comes when choosing foods that – rather than destroy our well-being – actually promote health and happiness. With several chronic, debilitating, and functionally impairing diseases including CVD and MDD on the rise, we ought to think about shifting our culture's outlook from “live to eat” to “eat to live.”

ACKNOWLEDGEMENTS

First and foremost, I would like to express my deep and sincere gratitude to my Advisor, Professor John F. Axelson, Ph.D., the "Fearless Leader," for his unwavering support, guidance, and constant encouragement throughout this thesis writing process. You have truly set an example of excellence as a researcher, mentor, and role model, all of which have deeply inspired me. I have not only gained a mentor but a dear friend. It has been a great honor and privilege to conduct research under your guidance.

Next, I would like to express my deepest appreciation to Professor Noah C. Berman, Ph.D., my reader, for his guidance and invaluable clinical expertise. When I took psychopathology, Professor Berman truly inspired me and helped me find my passion for the field of Psychiatry. Over my years at Holy Cross, he became a mentor and someone I look to for inspiration and guidance.

I would also like to extend my sincere gratitude to Dr. Xiaoduo Fan, M.D., M.P.H, M.S., Professor of Psychiatry at UMass Medical School and Director of Psychotic Disorders Clinical & Research Program, for his continuous support and immense knowledge, I sincerely appreciate him helping me find my passion for research and clinical medicine.

I am extremely grateful to my parents for their love, support, and sacrifices for educating and preparing me for my future. Also, I extend my heartfelt thanks to my friends who have provided me with encouragement and have cheered me on.

Finally, thank you to the College of the Holy Cross College Honors Program for the unique opportunity to write this thesis.

FIGURES

Figure 1

5 Major Food Categories in a Whole Food, Plant-Based Diet

Food Category	***Acceptable Foods***
Fruit	mangoes, bananas, grapes, strawberries, blueberries, oranges, cherries, etc.
Vegetables	lettuce, collard greens, broccoli, cauliflower, kale, carrots, etc.
Tubers & Starchy Vegetables	potatoes, yams, yucca, winter squash, corn, green peas, etc.
Whole Grains	millet, quinoa, barely, rice, whole wheat, oats, etc.
Legumes	kidney beans, chickpeas, lentils, lima beans, cannellini beans, black beans, etc.

Note. This figure shows the 5 major food categories allowed in a whole food, plant-based diet along with examples from each. The foods listed above have all been demonstrated to play a role in reducing inflammation.

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